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Practitioner's Docket No. U 011904-5 *PATENT*

4/7/99

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: VIDYA BRAJ LOHRAY, et al. Group No.: 1614
Serial No.: 09/179,002
Filed: OCTOBER 26, 1998 Examiner:
For: NEW HETEROCYCLIC COMPOUNDS AND THEIR USE IN MEDICINE, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

Assistant Commissioner for Patents
Washington, D.C. 20231

TRANSMITTAL OF CERTIFIED COPY

Attached please find the certified copy of the foreign application from which priority is claimed for this case:

Country:	INDIA
Application Number:	2420/MAS/97
Filing Date:	OCTOBER 27, 1997

WARNING: "When a document that is required by statute to be certified must be filed, a copy, including a photocopy or facsimile transmission of the certification is not acceptable." 37 C.F.R. 1.4(f) (emphasis added).

SIGNATURE OF PRACTITIONER

Reg. No.

JANET I. CORD
(type or print name of practitioner)

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NOTE: "The claim to priority need be in no special form and may be made by the attorney or agent, if the foreign application is referred to in the oath or declaration, as required by § 1.63." 37 C.F.R. 1.55(a).

CERTIFICATE OF MAILING (37 C.F.R. 1.8a)

I hereby certify that this correspondence is, on the date shown below, being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Signature

Date: JANUARY 5, 1999

JANET I. CORD
(type or print name of person certifying)

THE PATENTS ACT, 1970.

It is hereby Certified that annexed hereto is a True Copy of the Application on Form-1A and the Provisional Specification filed on 27-10-1997 in connection with Patent Application No. 2420/MAS/97 filed by Dr. Reddy's Research Foundation, 7-1-27, Ameerpet, Hyderabad - 500 016, Andhra Pradesh, South India.----------

----------In witness thereof I have hereunto set my hand

Dated this the 7th day of December, 1998.
16th day of Agr hayana,1920,
(SAKA)

S. Chandrasekaran

(S. Chandrasekaran)
DEPUTY CONTROLLER OF PATENTS & DESIGNS

ent Office,
nai.

FORM 1A

THE PATENTS ACT, 1970
APPLICATION FOR PATENT BY THE ASSIGNEE OF THE TRUE AND FIRST INVENTOR(S)
(See Section 7)

(To be made in triplicate and shall be accompanied by 3 copies of the Provisional Specification in Form 3 or the complete specification in Form 3A).

We, Dr. Reddy's Research Foundation, an Indian company having its registered office at 7-1-27, Ameerpet, Hyderabad, A.P., INDIA, 500 016 hereby declare

(i) that we are in possession of an invention for **NEW HETEROCYCLIC COMPOUNDS AND THEIR USE IN MEDICINE : PROCESS FOR THEIR PREPARATION & PHARMACEUTICAL COMPOSITIONS CONTAINING THEM.**

(ii) that we claim to be the assignees of :

VIDYA BHUSHAN LOHRAY, BRAJ BHUSHAN LOHRAY, PARASELLI BHEEMA RAO, RAMANUJAM RAJAGOPALAN, RANJAN CHARKRABARTI	All citizens & residents of India belonging to Dr. REDDY'S RESEARCH FOUNDATION, 7-1-27, AMEERPET HYDERABAD - 500 016.

who claim and are believed to be true and first inventors thereof.

(iii) that the provisional specification filed with this application and the complete specification and any amended specification which may hereafter be filed in this behalf will be, true of the invention to which this application relates ;

(iv) that we believe that we are entitled to a patent for the said invention having regard to the provisions of the Patent Act, 1970.

(v) that to the best of our knowledge, information and belief the facts and matters stated herein are correct and that there is no lawful ground of objection to the grant to us on this application.

We request that a patent may be granted to us for the said invention.

We also request you to accept this application as a **WTO application / Mail Box application**.

We request that all the notices, requisitions and communications relating to this application may be sent to

The President
Dr. Reddy's Research Foundation
7-1-27, Ameerpet
Hyderabad, A.P., 500 016

Dated this twenty second (22nd) day of October 1997

(Signed) _____
Dr. A. Venkateswarlu
President
Dr. Reddy's Research Foundation

The Controller of Patents
The Patents Office Branch
Chennai

ENDORSEMENT BY THE TRUE AND FIRST INVENTOR(s)

We, VIDYA BHUSHAN LOHRAY, BRAJ BHUSHAN LOHRAY, PARASELLI BHEEMA RAO, RAMANUJAM RAJAGOPALAN, RANJAN CHAKRABARTI, ALL citizens & residents of India, belonging to Dr. REDDY'S RESEARCH FOUNDATION, 7-1-27, AMEERPET, HYDERABAD-500 016, referred to on the reverse of this application as claiming to be the true and first inventor(s) hereby declare that the applicants who have signed this application on the reverse is our assignee.

Dated this twenty Secnd (22 nd) day of October 1997

(Signed) VidyaBhusha
VIDYA BHUSHAN LOHRAY

(Signed) B. Bhushan Lohray
BRAJ BHUSHAN LOHRAY

(Signed) P. Bheemarao
PARASELLI BHEEMA RAO

(Signed) Ramanujam Rajagopalan
RAMANUJAM RAJAGOPALAN

(Signed) Ranjan Chakrabarti
RANJAN CHAKRABARTI

Signature of two witnesses
along with their names & addresses :

1. _____
Dr. Swaminathan Subramaniam
Dr. Reddy's Research Foundation
Bollaram Road, Miyapur, Hyderabad - 500 050.

2. _____
Dr. S. Padmaja
Dr. Reddy's Research Foundation
Bollaram Road, Miyapur, Hyderabad - 500 050.

FORM 3

THE PATENT ACT, 1970

PROVISIONAL SPECIFICATION

(SECTION 10)

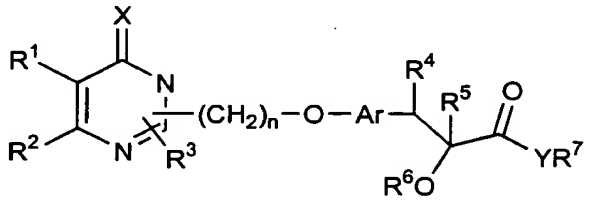
NEW HETEROCYCLIC COMPOUNDS AND THEIR USE IN MEDICINE ; PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

Dr. Reddy's Research Foundation,
an Indian Company having its registered office at
7-1-27, Ameerpet
Hyderabad - 500 016, A. P., INDIA

THE FOLLOWING SPECIFICATION DESCRI[BES THE NATURE OF THE INVENTION

Field of Invention

The present invention relates to novel hypoglycemic and hypocholesterolemic compounds, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates and pharmaceutically acceptable compositions containing them. More particularly, the present invention relates to novel β-aryl-α-oxysubstituted alkylcarboxylic acids of the general formula (I), their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates and pharmaceutically acceptable compositions containing them.



(I)

The present invention also relates to a process for the preparation of the above said novel compounds, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, novel intermediates and pharmaceutical compositions containing them.

The compounds of the present invention lower total cholesterol (TC); increase high density lipoprotein (HDL) and decrease low density lipoprotein (LDL), which have beneficial effect on coronary heart disease and atherosclerosis.

The compounds of general formula (I) are useful for the treatment and / or prophylaxis of diseases in which elevated cholesterol, elevated lipids and elevated free fatty acids are primary causes. Examples of these diseases are hypertension, coronary heart disease, atherosclerosis, stroke, peripheral vascular diseases and related disorders These compounds are useful for the treatment of familial hypercholesterolemia, hypertriglyceridemia, lowering of atherogenic lipoproteins, VLDL and LDL. The compounds of the present invention can be used for the treatment of certain renal diseases including glomerulonephritis, glomerularsclerosis, nephrotic syndrome, hypertensive nephrosclerosis. The compounds of general formula (I) are also useful for the treatment / prophylaxis of insulin resistance (type II diabetes), impaired glucose tolerance,

dyslipidemia, disorders related to syndrome X such as hypertension, coronary heart disease, and other cardiovascular disorders, obesity and also psoriasis, polycystic ovarian syndrome (PCOS). These compounds may also be useful as aldose reductase inhibitors, for improving cognitive functions in dementia and treating diabetic complications.

Background of Invention

Atherosclerosis and other peripheral vascular diseases are the major causes affecting the quality of life of millions of people. Therefore, considerable attention has been directed towards understanding the etiology of hypercholesterolemia and hyperlipidemia and development of effective therapeutic strategies.

Hypercholesterolemia has been defined as plasma cholesterol level that exceeds arbitrarily defined value called "normal" level. Recently, it has been accepted that "ideal" plasma levels of cholesterol are much below the "normal" level of cholesterol in general population and the risk of coronary artery disease (CAD) increases as cholesterol level rises above the "optimum" (or "ideal") value. There is clearly a definite cause and effect-relationship between hypercholesterolemia and CAD, particularly for individuals with multiple risk factors. Most of the cholesterol is present in the esterified forms with various lipoproteins such as Low density lipoprotein (LDL), Intermediate density lipoprotein (IDL), High density lipoprotein (HDL) and partially as Very low density lipoprotein (VLDL). Studies clearly indicate that there is an inverse correlationship between CAD and atherosclerosis with serum HDL-cholesterol concentrations. (Stampfer *et al., N. Engl. J. Med.,* **325** (1991), 373-381) and the risk of CAD increases with increasing levels of LDL and VLDL.

In CAD, generally "fatty streaks" in carotid, coronary and cerebral arteries, are found which are primarily free and esterified cholesterol. Miller *et al.,* (*Br. Med. J.,* **282** (1981), 1741 - 1744) have shown that increase in HDL-particles may decrease number of sites of stenosis in coronary arteries of human, and high level of HDL-cholesterol may protect against the progression of atherosclerosis. Picardo *et al.,* (*Arteriosclerosis* **6** (1986) 434 - 441) have shown by *in vitro* experiment that HDL is capable of removing cholesterol from cells. They suggest that HDL may deplete tissues of excess free cholesterol and transfer them to liver (Macikinnon *et al., J. Biol. chem.* **261** (1986), 2548 - 2552). Therefore, agents that increase HDL cholesterol

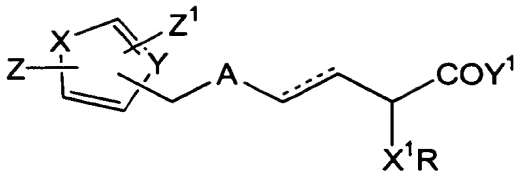
would have therapeutic significance for the treatment of hypercholesterolemia and coronary heart diseases (CHD).

Moreover, it has been well established that hyperlipidemia is the primary cause for cardiovascular diseases due to atherosclerosis. Numerous studies in recent years have been directed towards lowering plasma cholesterol, in particular, low density lipoprotein cholesterol for preventing cardiovascular diseases. Thus, the therapeutic agents which can increase HDL-cholesterol, decrease LDL-cholesterol, VLDL-cholesterol and triglyceride and reduce total cholesterol in plasma to bring within the "ideal" limit would be of great significance in managing cardiovascular diseases.

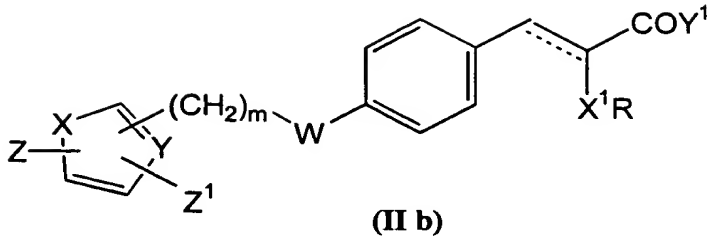
Diabetes and insulin resistance is yet another disease which severely effects the quality of a large population in the world. Insulin resistance is the diminished ability of insulin to exert its biological action across a broad range of concentrations. In insulin resistance, the body secretes abnormally high amounts of insulin to compensate for this defect; failing which, the plasma glucose concentration inevitably rises and develops into diabetes. Among the developed countries, diabetes mellitus is a common problem and is associated with a variety of abnormalities including obesity, hypertension, hyperlipidemia (J. Clin. Invest., (1985) 75 : 809 - 817; N. Engl. J. Med. (1987) 317 : 350 - 357 ; J. Clin. Endocrinol. Metab., (1988) 66 : 580 - 583; J. Clin. Invest., (1975) 68 : 957 - 969) and other renal complications (See Patent Application No. WO 95/21608). It is now increasingly being recognized that insulin resistance and relative hyperinsulinemia have a contributory role in obesity, hypertension, atherosclerosis and type 2 diabetes mellitus. The association of insulin resistance with obesity, hypertension and angina has been described as a syndrome having insulin resistance as the central pathogenic link-Syndrome-X.

A few β-aryl-α-hydroxy propionic acids and their derivatives, their analogs have been reported to be useful in the treatment of hyperglycemia and hypercholesterolemia. Some of such compounds described in the prior art are outlined below :

i) U.S. Pat. 5,306,726; PCT, WO91/19702 disclose several 3-aryl-2-hydroxypropionic acid derivatives of general formula (IIa) and (IIb) as hypolipidemic and hypoglycemic agents.

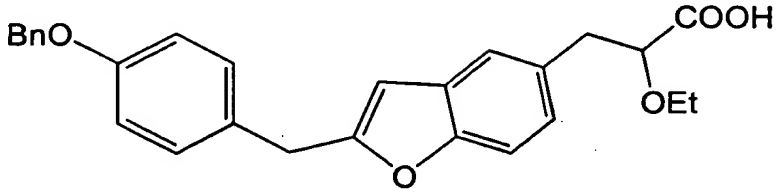


(II a)

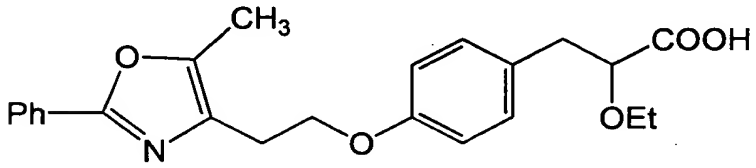


(II b)

Examples of these compounds are shown in formula (II c) and (II d)

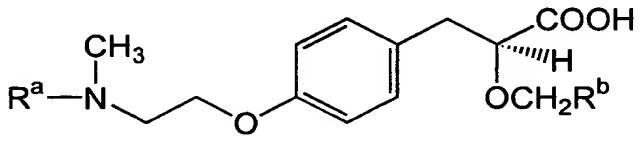


(II c)



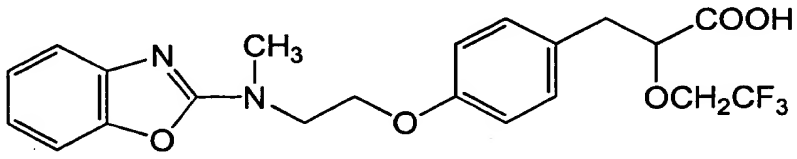
(II d)

ii) International Patent Applications, WO 95/03038 and WO 96/04260 disclose compounds of formula (II e)



(II e)

wherein R^a represents 2- benzoxazolyl or 2-pyridyl and R^b represent CF_3 or CH_2OCH_3 or CH_3. A typical example is (*S*)-3-[4-[2-[N-(2-benzoxazolyl]N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoic acid (II f).



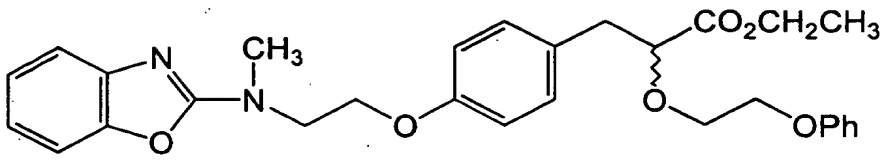
(II f)

iii) International Patent Application Nos. WO 94/13650, WO 94/01420 and WO 95/17394 disclose the compounds of general formula (II g)

$$A^1—X—(CH_2)_n—O—A^2—A^3—Y.\ R^2 \qquad \text{(II g)}$$

wherein A^1 represent aromatic heterocycle, A^2 represents substituted benzene ring and A^3 represents moiety of formula $(CH_2)_m$-CH-(OR^1), wherein R^1 represents alkyl groups, m is an integer; X represent substituted or unsubstituted N; Y represents C=O or C=S. R^2 represents

OR^3 where R^3 may be alkyl, aralkyl, aryl group. An example of these compounds is shown in formula (II h)



(II h)

Summary of the Invention

With an objective to develop novel compounds for the treatment of diseases related to Syndrome-X, hypercholesterolemia, atherosclerosis and coronary artery diseases with better efficacy, potency and lower toxicity, we focussed our research to develop new compounds which can decrease total cholesterol within the "ideal" limit and increase HDL cholesterol, which also would have beneficial effect in the treatment of hyperglycemia and hyperlipidemia. Effort in this direction has lead to compounds having general formula (I) as defined above.

The main objective of the present invention is therefore, to provide novel β-aryl-α-oxysubstituted alkylcarboxylic acids and their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates and pharmaceutical compositions containing them, or their mixtures.

Another objective of the present invention is to provide novel β-aryl-α-oxysubstituted alkylcarboxylic acids and their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates and pharmaceutical compositions containing them or their mixtures having enhanced activities, no toxic effect or reduced toxic effect.

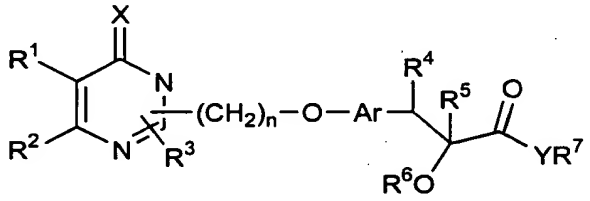
Yet another objective of the present invention is to produce a process for the preparation of novel β-aryl-α-oxysubstituted alkylcarboxylic acids and their derivatives of the formula

(I) as defined above, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts and their pharmaceutically acceptable solvates.

Still another objective of the present invention is to provide pharmaceutical compositions containing compounds of the general formula (I), their analogs, their derivatives, their tautomers, their stereoisomers, their polymorphs, their salts, solvates or their mixtures in combination with suitable carriers, solvents, diluents and other media normally employed in preparing such compositions.

Detailed Description of the Invention

α-Oxysubstituted propionic acids, their derivatives and their analogs of the present invention have the general formula (I)



(I)

In the above formula (I), X represents O or S ; the groups R^1, R^2 and group R^3 when present on carbon atom, may be same or different and represent hydrogen, halogen, hydroxy, cyano or nitro, or optionally substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, heterocyclyl, heteroaryl, heteroaralkyl, acyl, acyloxy, hydroxyalkyl, amino, acylamino, arylamino, aminoalkyl, aryloxy, alkoxycarbonyl, alkylamino, alkoxyalkyl, alkylthio, thioalkyl groups, carboxylic acid or its derivatives, or sulfonic acid or its derivatives; R^1, R^2 along with the adjacent atoms to which they are attached may also form a substituted or unsubstituted cyclic structure of from 5 or 6 atoms with one or more double bonds, the cyclic structure may be carbocyclic or may contain one or more heteroatoms selected from oxygen, nitrogen and sulfur; R^3 when attached to nitrogen atom represents hydrogen, hydroxy, or optionally substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, heterocyclyl, heteroaryl, heteroaralkyl, acyl, acyloxy, hydroxyalkyl, amino, acylamino, arylamino, aminoalkyl, aryloxy, alkoxycarbonyl, alkylamino, alkoxyalkyl, alkylthio, thioalkyl groups, carboxylic acid derivatives, or sulfonic acid derivatives. When the groups representing

R^1, R^2 or R^3 are substituted, the substituents are selected from the same groups that may represent R^1, R^2, and R^3 such as hydroxy, halogen, cyano or nitro, or optionally substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, heterocyclyl, heteroaryl, heteroaralkyl, acyl, acyloxy, hydroxyalkyl, amino, acylamino, arylamino, aminoalkyl, aryloxy, alkoxycarbonyl, alkylamino, alkoxyalkyl, alkylthio, thioalkyl groups, carboxylic acid or its derivatives, or sulfonic acid or its derivatives. The linking group represented by $-(CH_2)_n-O-$ in formula (I) may be attached either through nitrogen atom or through carbon atom where n is an integer ranging from 1 - 4. Ar represents an optionally substituted divalent aromatic or heterocyclic group, R^4 and R^5 may be same or different and represent hydrogen atom, halogen, lower alkyl, optionally substituted aralkyl group or forms a bond together; R^6 may be hydrogen or optionally substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, alkoxyalkyl, alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaralkyl groups; R^7 may be hydrogen or optionally substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaralkyl groups; Y represents oxygen or NR^8, where R^8 represents hydrogen, alkyl, aryl, heterocyclyl, aralkyl, heteroaralkyl groups; R^7 and R^8 together may form a 5 or 6 membered cyclic structure containing one or more heteroatoms selected from oxygen, sulfur or nitrogen;

Suitable groups represented by R^1, R^2, and the group R^3 when attached to carbon atom may be selected from hydrogen, halogen atom such as fluorine, chlorine, bromine, or iodine; hydroxy, cyano, nitro; substituted or unsubstituted (C_1-C_{12})alkyl group, especially, linear or branched (C_1-C_6)alkyl group, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, t-butyl, n-pentyl, isopentyl, hexyl and the like; cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like, cycloalkyl group may be substitued; cycloalkyloxy group such as cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy and the like, cycloalkyloxy group may be substituted; aryl group such as phenyl or naphthyl, the aryl group may be substituted; aralkyl such as benzyl or phenethyl, the aralkyl group may be substituted; heteroaryl group such as pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, tetrazolyl, benzopyranyl, benzofuranyl and the like, the heteroaryl group may be substituted; heterocyclyl groups such as aziridinyl, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl and the like, the heterocyclyl group may be substituted; aryloxy such as phenoxy, naphthyloxy, the aryloxy group may be substituted; alkoxycarbonyl such as methoxycarbonyl or ethoxycarbonyl; aryloxycarbonyl group such as optionally substituted phenoxycarbonyl, naphthyloxy carbonyl; aralkoxycarbonyl wherein the aryl moiety is phenyl or naphthyl such as

$PhCH_2OCO$, $PhCH_2CH_2OCO$, naphthyl CH_2OCO wherein the aryl moiety may be substituted; arylamino group such as HNC_6H_5, HNC_6H_4-Hal, HNC_6H_4-CH_3, HNC_6H_4-OCH_3, $NCH_3C_6H_5$ and the like; amino group; amino(C_1-C_6)alkyl; hydroxy(C_1-C_6)alkyl; (C_1-C_6)alkoxy; thio(C_1-C_6)alkyl; (C_1-C_6)alkylthio; acyl group such as acetyl, propionyl or benzoyl, the acyl group may be substituted; acylamino groups such as $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_6H_5$, aralkoxycarbonylamino group such as $NHCOOCH_2C_6H_5$, $HNCOOCH_2C_6H_4$-Hal, $HNCOOCH_2C_6H_4CH_3$, $HNCOOCH_2C_6H_4OCH_3$ and the like; wherein the aryl moiety may be substituted; alkoxycarbonyl amino group such as, $NHCOOC_2H_5$, $NHCOOCH_3$ and the like; carboxylic acid or its derivatives such as amides, like $CONH_2$, CONHMe, $CONMe_2$, CONHEt, $CONEt_2$, CONHPh and the like, the carboxylic acid derivatives may be substituted; acyloxy group such as MeCOO, EtCOO, PhCOO and the like, which may optionally be substituted; sulfonic acid or its derivatives such as SO_2NH_2, SO_2NHMe, SO_2NMe_2, SO_2NHCF_3 and the like, the sulfonic acid derivatives may be substituted.

When the groups represented by R^1, R^2 and the group R^3 when attached to carbon atom are substituted, the substituents may be selected from halogen, hydroxy, or nitro or optionally substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, heterocyclyl, heteroaryl, heteroaralkyl, acyl, acyloxy, hydroxyalkyl, amino, acylamino, arylamino, aminoalkyl, aryloxy, alkoxycarbonyl, alkylamino, alkoxyalkyl, alkylthio, thioalkyl groups, carboxylic acid or its derivatives, or sulfonic acid or its derivatives.

It is preferred that the substituents on R^1 - R^3 represent hydrogen, halogen atom such as fluorine, chlorine, bromine; alkyl group such as methyl, ethyl, isopropyl, n-propyl, n-butyl; cycloalkyl group such as cyclopropyl; aryl group such as phenyl; aralkyl group such as benzyl; (C_1-C_3)alkoxy, benzyloxy, hydroxy group, acyl or acyloxy groups.

Suitable R^3 when attached to nitrogen atom is selected from hydrogen, substituted or unsubstituted (C_1-C_{12})alkyl group, especially, linear or branched (C_1-C_6)alkyl group, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, t-butyl, n-pentyl, isopentyl, hexyl and the like; cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like; aryl group such as phenyl or naphthyl, the aryl group may be substituted; aralkyl group such as benzyl or phenethyl, the aralkyl group may be substituted; heteroaryl group such as pyridyl, thienyl, furyl and the like, the heteroaryl group may be substituted; alkoxycarbonyl such as methoxycarbonyl or ethoxycarbonyl; aryloxycarbonyl group such as optionally substituted phenoxycarbonyl; amino(C_1-C_6)alkyl; hydroxy(C_1-C_6)alkyl; thio(C_1-C_6)alkyl; acyl group such as acetyl, propionyl or benzoyl, the acyl group may be substituted.

When the groups represented by R^3 are substituted, preferred substituent is halogen such as fluorine, chlorine; hydroxy, acyl, acyloxy, amino groups.

n is an integer ranging from 1 - 4. It is preferred that n be 1 or 2.

It is preferred that the group represented by Ar be substituted or unsubstituted groups selected from divalent phenylene, naphthylene, pyridyl, quinolinyl, benzofuryl, dihydrobenzofuryl, benzopyranyl, indolyl, indolinyl, azaindolyl, azaindolinyl, pyrazolyl, benzothiazolyl, benzoxazolyl and the like. The substituents on the group represented by Ar may be selected from linear or branched $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_3)$alkoxy, halogen, acyl, amino, acylamino, thio or carboxylic or sulfonic acids and their derivatives.

It is more preferred that Ar represents substituted or unsubstituted divalent phenylene, naphthylene, benzofuryl, indolyl, indolinyl, quinolinyl, azaindolyl, azaindolinyl, benzothiazolyl or benzoxazolyl.

It is still more preferred that Ar is represented by divalent phenylene or naphthylene, which may be optionally substituted by methyl, halomethyl, methoxy or halomethoxy groups.

Suitable R^4 includes hydrogen, hydroxy, lower alkyl group such as methyl, ethyl or propyl; aralkyl group such as benzyl which may be optionally substituted; halogen atom such as fluorine, chlorine, bromine or iodine; or R^4 together with R^5 represents a bond.

It is preferred that R^4 represents hydrogen or a bond together with R^5.

Suitable R^5 represents hydrogen, hydroxy, lower alkyl group such as methyl, ethyl or propyl; aralkyl group such as benzyl which may be optionally substituted; halogen atom such as fluorine, chlorine, bromine or iodine; or together with R^4 forms a bond. It is preferred that R^5 represents hydrogen or a bond together with R^4.

Suitable groups represented by R^6 may be selected from hydrogen, linear or branched $(C_1\text{-}C_{16})$alkyl, preferably $(C_1\text{-}C_{12})$alkyl; aryl group such as phenyl, naphthyl; heteroaryl group such as pyridyl, thienyl, furyl and the like; aralkyl group wherein the alkyl moiety may contain $(C_1\text{-}C_6)$ atoms such as benzyl and phenethyl etc; heterocyclyl group such as aziridinyl, pyrrolidinyl, piperidinyl and the like; heteroaralkyl wherein the alkyl moiety may contain $(C_1\text{-}C_6)$atoms and heterocyclyl group may be pyridyl, furyl, thienyl, benzoxazolyl, benzothiazolyl, benzoxazinyl, benzothiazinyl and the like; $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl group such as methoxymethyl, ethoxymethyl, methoxyethyl, ethoxypropyl and the like; acyl group such as acetyl, propanoyl, butyroyl, benzoyl and the like; $(C_1\text{-}C_6)$alkoxycarbonyl, the alkyl group may be substituted; aryloxycarbonyl such as phenoxycarbonyl, naphthyloxycarbonyl, the aryl group may be

substituted; (C_1-C_6)alkylaminocarbonyl, the alkyl group may be substituted; arylaminocarbonyl such as PhNHCO, naphthylaminocarbonyl, the aryl moiety may be substituted.

Suitable groups represented by R^7 may be selected from hydrogen, linear or branched (C_1-C_{16})alkyl, preferably (C_1-C_{12})alkyl group such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, pentyl, hexyl, octyl and the like; (C_3-C_7)cycloalkyl such as cyclopropyl, cyclopentyl, cyclohexyl and the like; aryl group such as phenyl, naphthyl; heteroaryl group such as pyridyl, thienyl, furyl and the like; aralkyl group such as benzyl and phenethyl; heterocyclyl group such as aziridinyl, pyrrolidinyl, piperidinyl and the like.

Suitable groups represented by R^8 may be selected from hydrogen, linear or branched (C_1-C_{16})alkyl, preferably (C_1-C_{12})alkyl; aryl group such as phenyl, naphthyl; heterocyclyl such as pyridyl, thienyl, furyl, oxazolyl, pyrrolyl, aziridinyl, pyrrolidinyl, morpholinyl, piperidinyl and the like; heteroaralkyl wherein the alkyl moiety may be (C_1-C_6)alkylene and the heteroaryl group may be benzoxazinyl, benzothiazinyl, pyridyl, furyl, thienyl, oxazolyl, thiazolyl, pyrrolyl and the like; aralkyl group such as benzyl and phenethyl.

Suitable ring structures formed by R^7 and R^8 together may be selected from pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl and the like.

Suitable n is an integer ranging from 1 to 4, preferably n represents an integer 1 or 2.

Pharmaceutically acceptable salts forming part of this invention include salts of the azolidinedione moiety such as alkali metal salts like Li, Na, and K salts, alkaline earth metal salts like Ca and Mg salts, salts of organic bases such as lysine, arginine, guanidine, diethanolamine, choline and the like, ammonium or substituted ammonium salts, salts of carboxy group wherever appropriate, such as aluminum, alkali metal salts; alkaline earth metal salts, ammonium or substituted ammonium salts. Salts may include acid addition salts which are, sulphates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates, tartrates, maleates, citrates, succinates, palmoates, methanesulfonates, benzoates, salicylates, hydroxynaphthoates, benzenesulfonates, ascorbates, glycerophosphates, ketoglutarates and the like. Pharmaceutically acceptable solvates may be hydrates or comprising other solvents of crystallization such as alcohols.

Particularly useful compounds according to the present invention includes:

2-Ethoxy-3[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl]propionic acid

(+)-2-Ethoxy-3[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl]propionic acid

(-)-2-Ethoxy-3[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl]propionic acid

2-Ethoxy-5-[[4-[4-oxo-3,4-dihydro-3-benzoxazenyl]methoxy]phenyl]propionic acid

(+)-2-Ethoxy-5-[[4-[4-oxo-3,4-dihydro-3-benzoxazenyl]methoxy]phenyl]propionic acid

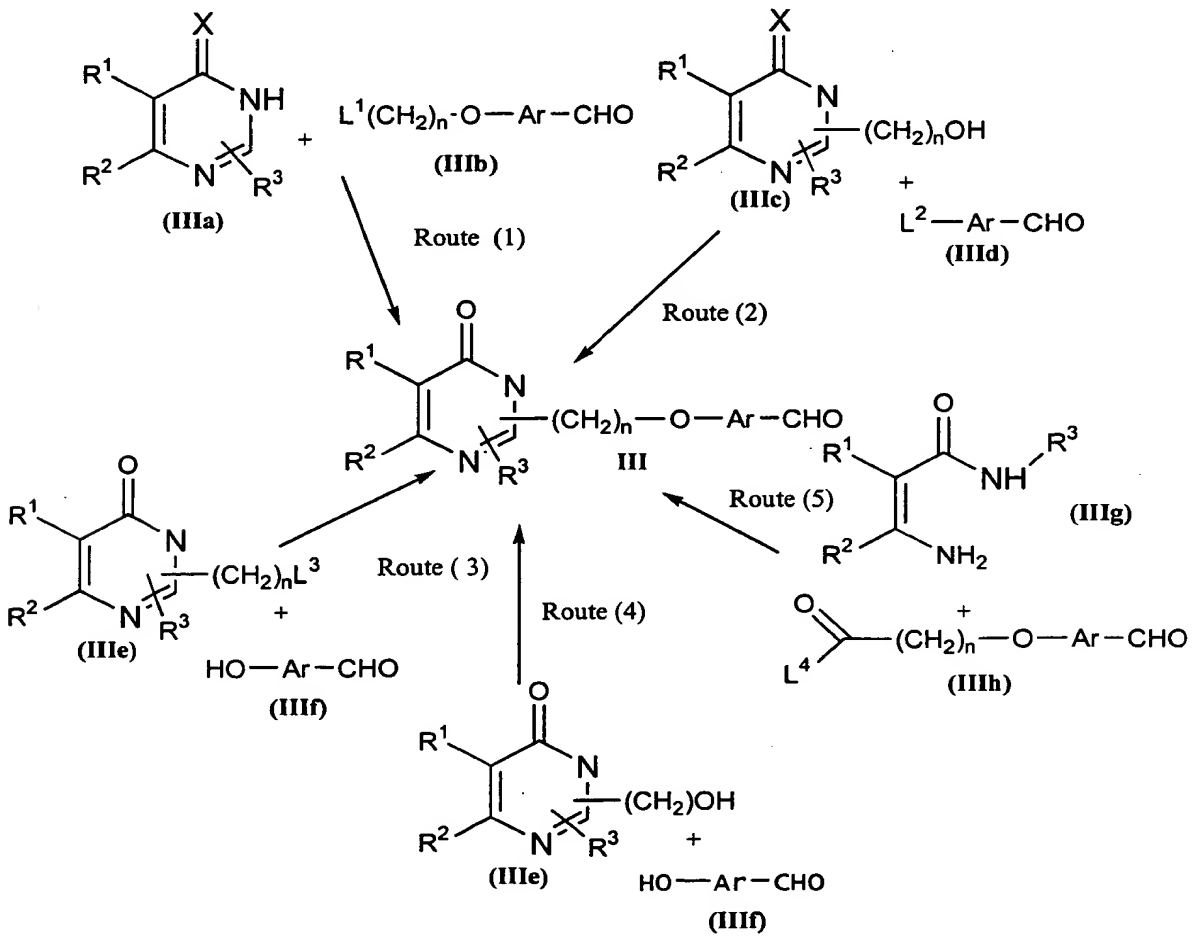
(-)-2-Ethoxy-5-[[4-[4-oxo-3,4-dihydro-3-benzoxazenyl]methoxy]phenyl]propionic acid

2-methoxyethyl-3[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl]propionic acid

(+)-2-methoxyethyl-3[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl]propionic acid

(-)-2-methoxyethyl-3[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl]propionic acid

The intermediate of formula (III) and process for its preparation has been disclosed in the copending application no. 1150/MAS/96. Various methods of its preparation are outlined in scheme-I.



Scheme-I

Route (1) : The reaction of a compound of general formula (IIIa) where all symbols are as defined earlier with a compound of general formula (IIIb) where L^1 is a leaving group to produce a compound of general formula (III) may be carried out in the presence of solvents such as DMSO, DMF, DME, THF, dioxane, ether and the like or a combination thereof. The reaction may be carried out in an inert atmosphere which may be maintained by using inert gases such as N_2, Ar, He. The reaction may be effected in the presence of a base such as alkalis like sodium hydroxide, potassium hydroxide, alkali metal carbonates like sodium carbonate, potassium carbonate; alkali metal hydrides such as sodium hydride or potassium hydride; organometallic bases like n-butyl lithium, alkali metal amides like sodamide or mixtures thereof. The amount of base may range from 1 to 5 equivalents, based on the amount of the compound of formula (IIIa), preferably the amount of base ranges from 1 to 3 equivalents. 1 to 3 equivalents of alkali metal halides based on the amount of compound of formula (IIIa) such as lithium bromide may be added as an additive. The reaction may be carried out at a temperature in the range of 0 ^oC to 150 ^oC, preferably at a temperature in the range of 15 ^oC to 100 ^oC. The duration of the reaction may range from 0.25 to 24 hours, preferably from 0.25 to 6 hours.

Route (2) : The reaction of compound of formula (IIIc) where all symbols are as defined earlier, with the compound of formula (IIId) where L^2 is hydroxy or halogen atom to produce a compound of formula (III) may be carried out in the presence of solvents such as THF, DMF, DMSO, DME and the like. The inert atmosphere may be maintained by using inert gases such as N_2, Ar or He. The reaction may be effected in the presence of a base such as K_2CO_3, Na_2CO_3, NaH. The reaction temperature may range from 20 ^oC to 150 ^oC, preferably at a temperature in the range of 30 ^oC to 100 ^oC. The duration of the reaction may range from 1 to 24 hours, preferably from 2 to 6 hours.

Route (3) : The reaction of compound of formula (IIIe) where all symbols are as defined earlier & L^3 is a leaving group auch as Cl, Br, I, OMs, OTs, OTf, and the like, with compound of formula (IIIf) to produce a compound of the formula (III) may be carried out in the presence of solvents such as THF, DMF, DMSO, DME and the like or mixtures thereof. The reaction may be carried out in an inert atmosphere which may be maintained by using inert gases such as N_2, Ar, or He. The reaction may be effected in the presence of a base such as K_2CO_3, Na_2CO_3 or

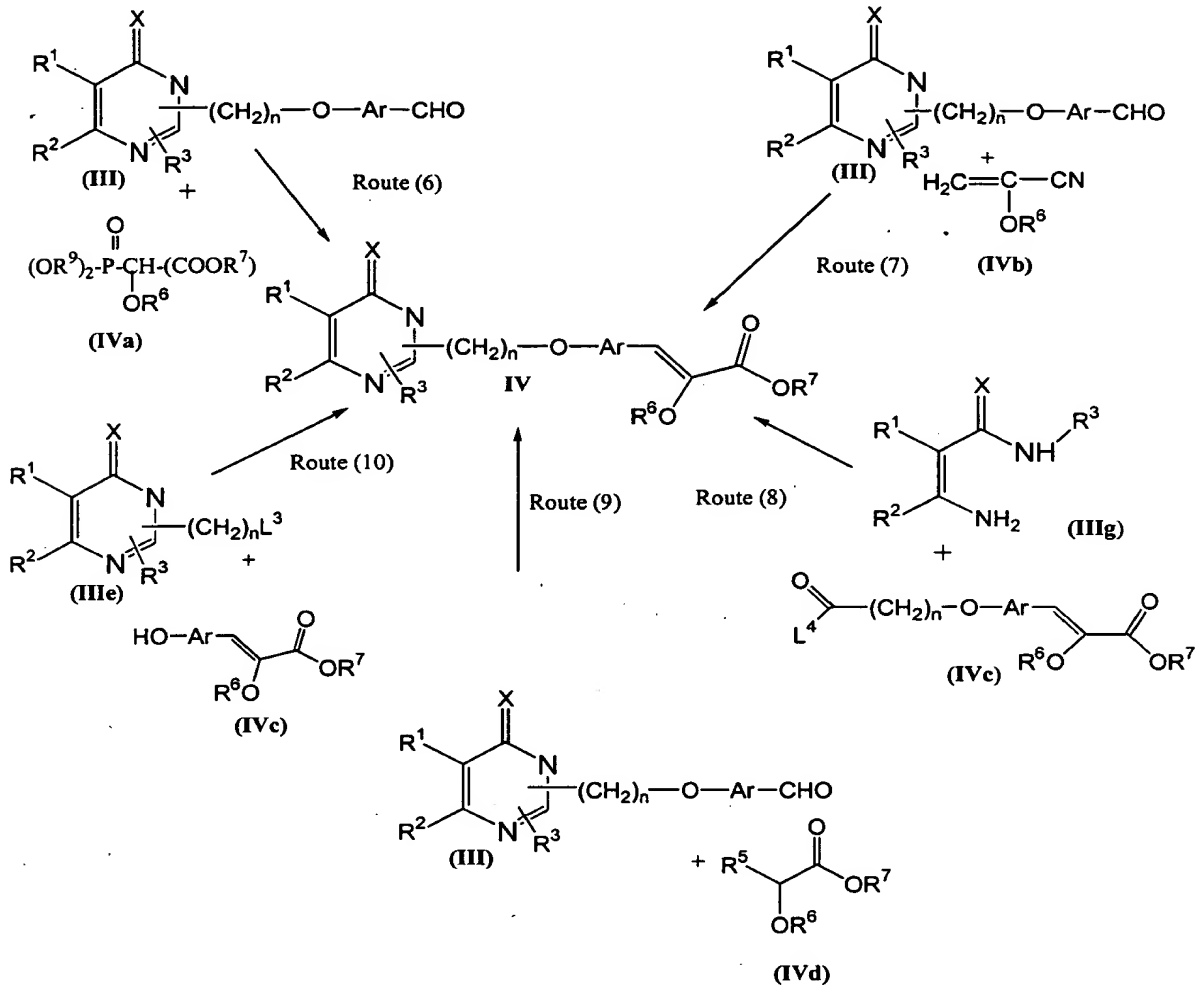
NaH or mixtures thereof. The reaction temperature may range from 20 °C - 120 °C, preferably at a temperature in the range of 30 °C - 100 °C. The duration of the reaction may range from 1 to 12 hours, preferably from 2 to 6 hours.

Route (4) : The reaction of compound of general formula (IIIe) where all symbols are as defined earlier, with a compound of general formula (IIIf) may be carried out using suitable coupling agents such as dicyclohexyl urea, triarylphosphine / dialkylazadicarboxylate such as PPh_3 / DEAD and the like. The reaction may be carried out in the presence of solvents such as THF, DME, CH_2Cl_2, $CHCl_3$, toluene, acetonitrile, carbontetrachloride and the like. The inert atmosphere may be maintained by using inert gases such as N_2, Ar, He. The reaction may be effected in the presence of DMAP, HOBT and they may be used in the range of 0.05 to 2 equivalents, preferably 0.25 to 1 equivalents. The reaction temperature may be in the range of 0 °C to 100 °C, preferably at a temperature in the range of 20 °C to 80 °C. The duration of the reaction may range from 0.5 to 24 hours, preferably from 6 to 12 hours.

Route (5) : The reaction of compound of general formula (IIIg) as defined above with a compound of general formula (IIIh) where all symbols are as defined earlier, L^4 is halogen, -OR^9, -O-C(=O)-OR^9, where R^9 is (C_1-C_5)alkyl, to produce a compound of general formula (III) may be carried out in neat or in the presence of solvents such as xylene, toluene, THF, dioxane, acetic acid, DMF, DMSO and the like or mixtures thereof. The reaction may be carried out in an inert atmosphere which may be maintained by using inert gases such as N_2, Ar or He. The reaction may be carried out at a temperature in the range of 50 °C to 200 °C, preferably at a temperature in the range of 60 ° C to 180 °C. The reaction may be effected in the presence or in absence of a base or an acid. The nature of the base or the acid is not critical. Example of such bases include organic bases such as pyridine, lutidine, triethyl amine, diisopropylethyl amine and the like, metal carbonates such as K_2CO_3, Na_2CO_3. Examples of acids include organic acids such as AcOH, C_2H_5COOH, butyric acid, p-toluenesulfonic acid, benzenesulfonic acid and the like, mineral acids such as HCl, HBr etc. The duration of the reaction may range from 0.25 to 48 hours, preferably from 0.50 to 18 hours.

In another embodiment of the present invention, the compound of general formula (IV) where R^1, R^2, R^3, R^4, R^6, R^7, X, n and Ar are as defined earlier, can be prepared by any of the

following routes shown in Scheme II. The compound of general formula (IV) represent compound of general formula (I), wherein all the symbols are as defined and R^4 and R^5 together represent a bond.



Scheme - II

Route (6) : The reaction of a compound of the general formula (III) as defined earlier with a compound of formula (IVa) where R^6, R^7 are as defined earlier and R^9 represents $(C_1\text{-}C_6)$alkyl, to yield compound of general formula (IV) may be carried out neat in the presence of a base such as alkali metal hydrides like NaH, KH or organolithiums like CH_3Li, BuLi and the like or alkoxides such as NaOMe, NaOEt,, K^+BuO^- or mixtures thereof. The reaction may be carried out in presence of solvents such as THF, dioxane, DMF, DMSO, DME and the like or mixtures thereof. HMPA may be used as cosolvent. The reaction temperature may range from -78 °C to 50 °C, preferably at a temperature in the range of -10 °C to 30 °C.

Route (7) : The reaction of a compound of the general formula (III) as defined above with a compound of formula (IVb) where R^6 is as defined earlier to yield compound of general formula (IV) may be carried out neat in the presence of a base such as alkali metal hydrides like NaH, KH. The reaction may be carried out in presence of solvents such as THF, dioxane, DMF, DMSO, DME and the like or mixtures thereof. The reaction temperature may range from 25 °C to 100 °C, preferably at a temperature in the range of 50 °C to 100 °C.

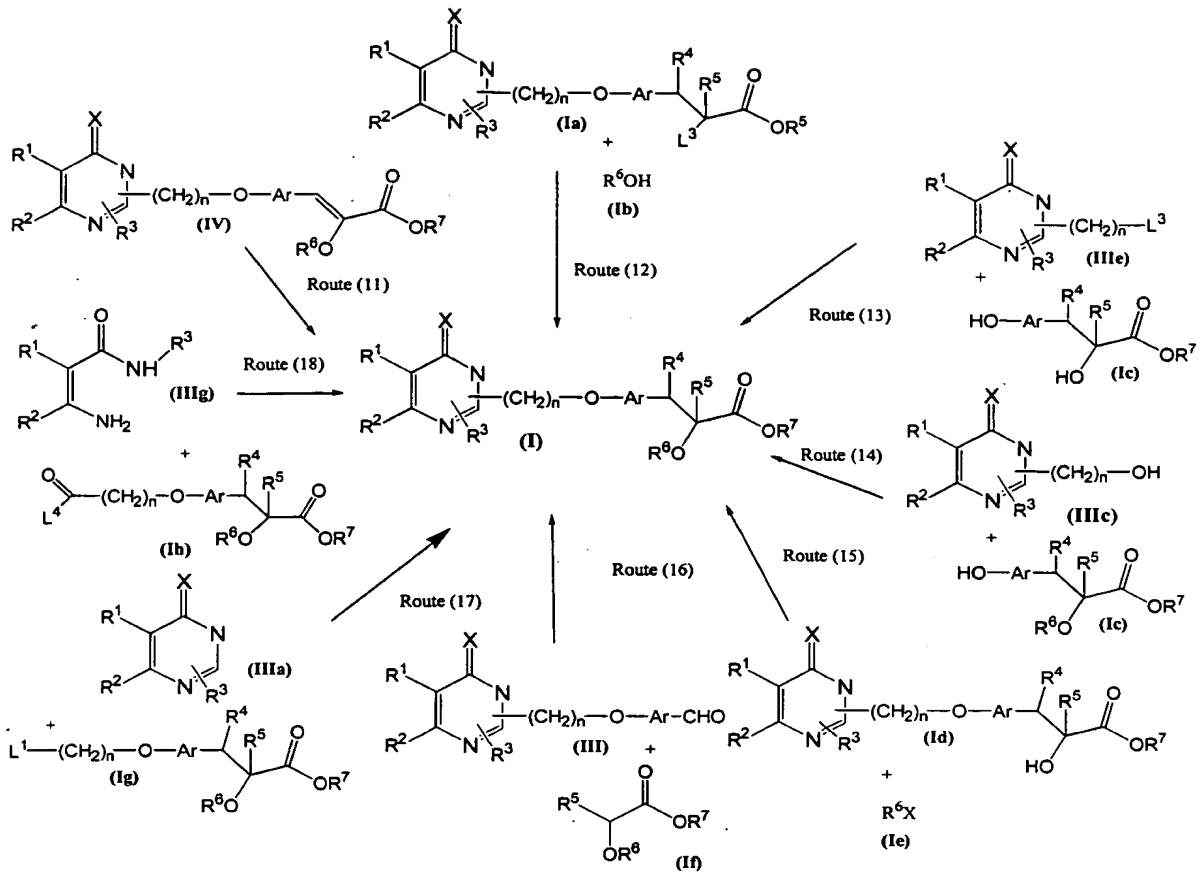
Route (8) : The reaction of compound of general formula (IIIg) defined earlier with a compound of general formula (IVc) where R^6, R^7 and Ar are as defined earlier & L^4 is halogen, $-OR^{10}$, $-O-C(=O)-OR^{10}$, where R^{10} is (C_1-C_5)alkyl, to produce a compound of general formula (IV) may be carried out in neat or in the presence of solvents such as xylene, toluene, THF, dioxane, acetic acid, DMF, DMSO and the like or mixtures thereof. The reaction may be carried out in an inert atmosphere which may be maintained by using inert gases such as N_2, Ar or He. The reaction may be carried out at a temperature in the range of 50 °C to 200 °C, preferably at a temperature in the range of 60 ° C to 180 °C. The reaction may be effected in the presence or in absence of a base or an acid. The nature of the base or the acid is not critical. Example of such bases include organic bases such as pyridine, lutidine, triethyl amine, diisopropylethyl amine and the like, metal carbonates such as K_2CO_3, Na_2CO_3. Examples of acids include organic acids such as AcOH, C_2H_5COOH, butyric acid, p-toluenesulfonic acid, benzenesulfonic acid and the like, mineral acids such as HCl, HBr etc. The duration of the reaction may range from 0.25 to 48 hours, preferably from 0.50 to 18 hours.

Route (9) : The reaction of a compound of the general formula (III) where all other symbols are as defined earlier, with a compound of formula (IVd) where R^5, R^6, R^7 are as defined earlier may be carried out under conventional conditions. The base is not critical. Any base normally employed for aldol condensation reaction may be employed, metal hydride such as NaH, KH, metal alkoxides such as NaOMe, K^+BuO^-, NaOEt, metal amides such as $LiNH_2$, $LiN(ipr)_2$. Aprotic solvent such as THF may be used. Inert atmosphere may be employed such as argon and the reaction is more effective under anhydrous conditions. Temperature in the range of -80 °C to 25 °C may be used. The β-hydroxy product may be dehydrated under conventional dehydration conditions such as treating with PTSA in solvents such as benzene or toluene. Temperature in the

range of 25 °C to reflux temperature of the solvent used may be employed, preferably at reflux temperature of the solvent by continous removal of water using a Dean Stark water separator.

Route (10) : The reaction of compound of formula (IIIe) defined earlier with compound of formula (IVc) where R^6, R^7 and Ar are as defined earlier to produce a compound of the formula (IV) may be carried out in the presence of solvents such as THF, DMF, DMSO, DME and the like or mixtures thereof. The reaction may be carried out in an inert atmosphere which may be maintained by using inert gases such as N_2, Ar, or He. The reaction may be effected in the presence of a base such as K_2CO_3, Na_2CO_3 or NaH or mixtures thereof. The reaction temperature may range from 20 °C - 120 °C, preferably at a temperature in the range of 30 °C - 100 °C. The duration of the reaction may range from 1 to 12 hours, preferably from 2 to 6 hours.

In yet another embodiment of the present invention, the compound of the general formula (I) where R^1 - R^7, X, n and Ar can be prepared by one or more of the processes shown in Scheme - III:



Scheme - III

Route (11) : The reduction of compound of the formula (IV) obtained as described earlier, to yield a compound of the general formula (I) where R^4 and R^5 each represent hydrogen atom and all symbols are as defined earlier, may be carried out in the presence of gaseous hydrogen and a catalyst such as Pd/C, Rh/C, Pt/C, and the like. Mixtures of catalysts may be used. The reaction may also be conducted in the presence of solvents such as dioxane, acetic acid, ethyl acetate and the like. A pressure between atmospheric pressure and 80 psi may be employed. The catalyst may be 5 - 10 % Pd/C and the amount of catalyst used may range from 50 - 300 % w/w. The reaction may also be carried out by employing metal solvent reduction such as magnesium in methanol or sodium amalgam in methanol.

Route (12) : The reaction of compound of formula (Ia) where all symbols are as defined earlier and L^3 is a leaving group such as halogen atom with an alcohol of general formula (Ib), where R^6 is as defined earlier to produce a compound of the formula (I) may be carried out in the presence of solvents such as THF, DMF, DMSO, DME and the like or mixtures thereof. The reaction may be carried out in an inert atmosphere which may be maintained by using inert gases such as N_2, Ar, or He. The reaction may be effected in the presence of a base such as KOH, NaOH, NaOMe,

NaOEt, K^+BuO^- or NaH or mixtures thereof. Phase transfer catalysts such as tetraalkylammonium halides or hydroxides may be employed. The reaction temperature may range from 20 °C - 120 °C, preferably at a temperature in the range of 30 °C - 100 °C. The duration of the reaction may range from 1 to 12 hours, preferably from 2 to 6 hours. The compound of general formula (Ia) and its preparation has been disclosed in the copending application No. 1150/MAS/96.

Route (13) : The reaction of compound of formula (IIIe) defined earlier with compound of formula (Ic) where all symbols are as defined earlier to produce a compound of the formula (I) may be carried out in the presence of solvents such as THF, DMF, DMSO, DME and the like or mixtures thereof. The reaction may be carried out in an inert atmosphere which is maintained by using inert gases such as N_2, Ar or He. The reaction may be effected in the presence of a base such as K_2CO_3, Na_2CO_3 or NaH or mixtures thereof. The reaction temperature may range from 20 °C - 120 °C, preferably at a temperature in the range of 30 °C - 80 °C. The duration of the reaction may range from 1 to 12 hours, preferably from 2 to 6 hours.

Route (14) : The reaction of compound of general formula (IIIc) defined earlier with a compound of general formula (Ic) where all symbols are as defined earlier may be carried out using suitable coupling agents such as dicyclohexyl urea, triarylphosphine/dialkylazadicarboxylate such as PPh_3 / DEAD and the like. The reaction may be carried out in the presence of solvents such as THF, DME, CH_2Cl_2, $CHCl_3$, toluene, acetonitrile, carbontetrachloride and the like. The inert atmosphere may be maintained by using inert gases such as N_2, Ar, He. The reaction may be effected in the presence of DMAP, HOBT and they may be used in the range of 0.05 to 2 equivalents, preferably 0.25 to 1 equivalents. The reaction temperature may be in the range of 0 °C to 100 °C, preferably at a temperature in the range of 20 °C to 80 °C. The duration of the reaction may range from 0.5 to 24 hours, preferably from 6 to 12 hours.

Route (15) : The reaction of compound of formula (Id) where all symbols are as defined earlier with a compound of formula (Ie) where R^6 is as defined earlier to produce a compound of formula (I) may be carried out in the presence of solvents such as THF, DMF, DMSO, DME and the like. The inert atmosphere may be maintained by using inert gases such as N_2, Ar or He. The reaction may be effected in the presence of a base such as KOH, NaOH, NaOMe, K^+BuO^-, NaH and the like. Phase transfer catalyst such as tetraalkylammoniumhalides or hydroxides may be employed. The reaction temperature may range from 20 °C to 150 °C, preferably at a

temperature in the range of 30 °C to 100 °C. The duration of the reaction may range from 1 to 24 hours, preferably from 2 to 6 hours.

The compound of formula (Id) represents compound of formula (I) where R^6 is hydrogen atom, Y is oxygen atom and all other symbols are as defined earlier.

The compound of general formula (Id) may also be prepared from compound of formula (Ia), described in copending application No. 1150/MAS/96, where L^3 is a halogen atom by reacting with formamide in the presence of water. Alternatively, it can be prepared from (Ia) by heating with aqueous alkali to 20 °C to 100 °C followed by reesterification of the hydrolysed acid.

Route (16) : The reaction of a compound of the general formula (III) as defined above with a compound of formula (If) where R^5, R^6, R^7 are as defined earlier may be carried out under conventional conditions. The base is not critical. Any base normally employed for aldol condensation reaction may be employed, metal hydride such as NaH, KH, metal alkoxides such as NaOMe, K^tBuO^-, NaOEt, metal amides such as $LiNH_2$, $LiN(ipr)_2$. Aprotic solvent such as THF may be used. Inert atmosphere may be employed such as argon and the reaction is more effective under anhydrous conditions. Temperature in the range of -80 °C to 25 °C may be used. The β-hydroxyaldol product may be dehydroxylated using conventional methods, conveniently by ionic hydrogentation technique such as by treating with a trialkyl silane in the presence of an acid such as trifluoroacetic acid. Solvent such as CH_2Cl_2 may be used. Favorably reaction proceeds at 25 °C. Higher temperature may be employed if the reaction is slow.

Route (17) : The reaction of a compound of general formula (IIIa) where all symbols are as defined earlier with a compound of general formula (Ig) where L^1 is a leaving group and all other symbols are as defined earlier to produce a compound of general formula (I) may be carried out in the presence of solvents such as DMSO, DMF, DME, THF, dioxane, ether and the like or a combination thereof. The reaction may be carried out in an inert atmosphere which may be maintained by using inert gases such as N_2, Ar, He. The reaction may be effected in the presence of a base such as alkalis like sodium hydroxide, potassium hydroxide, alkali metal carbonates like sodium carbonate, potassium carbonate; alkali metal hydrides such as sodium hydride or potassium hydride; organometallic bases like n-butyl lithium, alkali metal amides like sodamide or mixtures thereof. The amount of base may range from 1 to 5 equivalents, based on the amount of the compound of formula (IIIa), preferably the amount of base ranges from 1 to 3 equivalents. The reaction may be carried out at a temperature in the range of 0 °C to 150 °C, preferably at a

temperature in the range of 15 °C to 100 °C. The duration of the reaction may range from 0.25 to 24 hours, preferably from 0.25 to 6 hours.

Route (18) : The reaction of compound of general formula (IIIg) as defined above with a compound of general formula (Ih) where all symbols are as defined earlier, L^4 is halogen, $-OR^9$, $-O-C(=O)-OR^9$, where R^9 is (C_1-C_5)alkyl, to produce a compound of general formula (III) may be carried out in neat or in the presence of solvents such as xylene, toluene, THF, dioxane, acetic acid, DMF, DMSO and the like or mixtures thereof. The reaction may be carried out in an inert atmosphere which may be maintained by using inert gases such as N_2, Ar or He. The reaction may be carried out at a temperature in the range of 50 °C to 200 °C, preferably at a temperature in the range of 60 ° C to 180 °C. The reaction may be effected in the presence or in absence of a base or an acid. The nature of the base or the acid is not critical. Example of such bases include organic bases such as pyridine, lutidine, triethyl amine, diisopropylethyl amine and the like, metal carbonates such as K_2CO_3, Na_2CO_3. Examples of acids include organic acids such as AcOH, C_2H_5COOH, butyric acid, p-toluenesulfonic acid, benzenesulfonic acid and the like, mineral acids such as HCl, HBr etc. The duration of the reaction may range from 0.25 to 48 hours, preferably from 0.50 to 18 hours.

The compound of general formula (I) where Y represents oxygen may be converted to compound of formula (I), where Y represents NR^{12} using conventional reaction conditions using appropriate amines.

The pharmaceutically acceptable salts are prepared by reacting the compound of formula (I) with 1 to 4 equivalents of a base such as sodium hydroxide, sodium methoxide, sodium hydride, potassium t-butoxide, calcium hydroxide, magnesium hydroxide and the like, in solvents like ether, THF, methanol, t-butanol, dioxane, isopropanol, ethanol etc. Mixture of solvents may be used. Organic bases like lysine, arginine, diethanolamine, choline, guanidine and their derivatives etc. may also be used. Alternatively, acid addition salts are prepared by treatment with acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, p-toluenesulphonic acid, methanesulfonic acid, acetic acid, citric acid, maleic acid salicylic acid, hydroxynaphthoic acid, ascorbic acid, palmitic acid, succinic acid, benzoic acid, benzenesulfonic acid, tartaric acid and the like in solvents like ethyl acetate, ether, alcohols, acetone, THF, dioxane etc. Mixture of solvents may also be used.

The stereoisomers of the compounds forming part of this invention may be prepared by using reactants in their single enantiomeric form in the process wherever possible or by conducting the reaction in the presence of reagents or catalysts in their single enantiomer form or by resolving the mixture of stereoisomers by conventional methods. Some of the preferred methods include use of microbial resolution, resolving the diastereomeric salts formed with chiral acids such as mandelic acid, camphorsulfonic acid, tartaric acid, lactic acid, aminoalcohols derived from natural amino acids and the like or chiral bases such as brucine, cinchona alkaloids and their derivatives and the like.

Various polymorphs of compound of general formula (I) forming part of this invention may be prepared by crystallization of compound of formula (I) under different conditions. For example, using different solvents commonly used or their mixtures for recrystallization; crystallizations at different temperatures; various modes of cooling, ranging from very fast to very slow cooling during crystallizations. Polymorphs may also be obtained by heating or melting the compound followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe nmr spectroscopy, ir spectroscopy, differential scanning calorimetry, powder X-ray diffractogram or such other techniques.

The present invention also provides a pharmaceutical composition, containing the compounds of the general formula (I), as defined above, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates in combination with the usual pharmaceutically employed carriers, diluents and the like, useful for the treatment and / or prophylaxis of diseases in which elevated cholesterol, elevated lipids and elevated free fatty acids are primary causes. Examples of these diseases are hypertension, coronary heart disease, atherosclerosis, stroke, peripheral vascular diseases and related disorders These compounds are useful for the treatment of familial hypercholesterolemia, hypertriglyceridemia, lowering of atherogenic lipoproteins, VLDL and LDL. The compounds of the present invention can be used for the treatment of certain renal diseases including glomerulonephritis, glomerularsclerosis, nephrotic syndrome, hypertensive nephrosclerosis. The compounds of general formula (I) are also useful for the treatment / prophylaxis of insulin resistance (type II diabetes), impaired glucose tolerance, dyslipidemia, disorders related to syndrom X such as hypertension, coronary heart disease, obesity, psoriasis, polycystic ovarian syndrome (PCOS) and other cardiovascular disorders. These compounds may also be useful as aldose reductase inhibitors, for improving cognitive functions in dementia and treating diabetic complications.

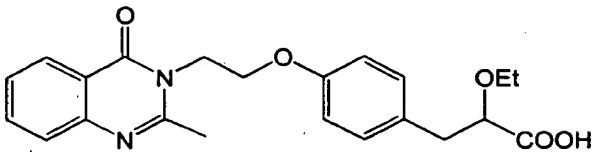
The pharmaceutical composition may be in the forms normally employed, such as tablets, capsules, powders, syrups, solutions, suspensions and the like, may contain flavourants, sweeteners etc. in suitable solid or liquid carriers or diluents, or in suitable sterile media to form injectable solutions or suspensions. Such compositions typically contain from 1 to 20 %, preferably 1 to 10 % by weight of active compound, the remainder of the composition being pharmaceutically acceptable carriers, diluents or solvents.

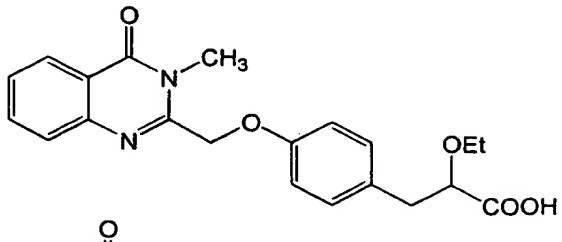
The compound of the formula (I) as defined above are clinically administered to mammals, including man, via either oral or parenteral routes. Administration by the oral route is preferred, being more convenient and avoiding the possible pain and irritation of injection. However, in circumstances where the patient cannot swallow the medication, or absorption following oral administration is impaired, as by disease or other abnormality, it is essential that the drug be administered parenterally. By either route, the dosage is in the range of about 0.10 to about 100 mg / kg body weight of the subject per day or preferably about 0.10 to about 30 mg / kg body weight per day administered singly or as a divided dose. However, the optimum dosage for the individual subject being treated will be determined by the person responsible for treatment, generally smaller doses being administered initially and thereafter increments made to determine the most suitable dosage.

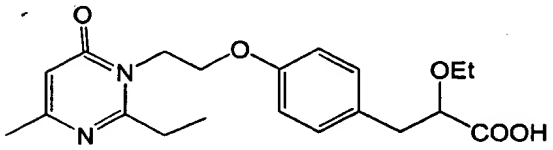
Suitable pharmaceutically acceptable carriers include solid fillers or diluents and sterile aqueous or organic solutions. The active compound will be present in such pharmaceutical compositions in the amounts sufficient to provide the desired dosage in the range as described above. Thus, for oral administration, the compounds can be combined with a suitable solid or liquid carrier or diluent to form capsules, tablets, powders, syrups, solutions, suspensions and the like. The pharmaceutical compositions, may, if desired, contain additional components such as flavourants, sweeteners, excipients and the like. For parenteral administration, the compounds can be combined with sterile aqueous or organic media to form injectable solutions or suspensions. For example, solutions in sesame or peanut oil, aqueous propylene glycol and the like can be used, as well as aqueous solutions of water-soluble pharmaceutically-acceptable acid addition salts or salts with base of the compounds. The injectable solutions prepared in this manner can then be administered intravenously, intraperitoneally, subcutaneously, or intramuscularly, with intramuscular administration being preferred in humans.

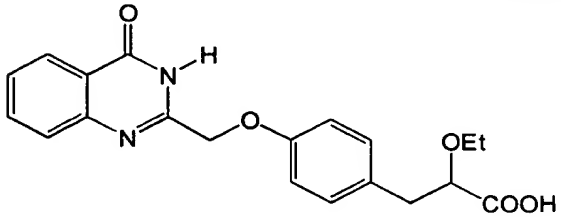
The compounds of the present invention showed improved random blood sugar, triglyceride as well as cholesterol lowering activities and HDL increasing ability. This was demonstrated by *in vivo* animal experiments.

Following are a few compounds prepared by the process described in this invention :









Dated this twenty Second (22nd) day of October 1997.

Dr. A. Venkateswarlu
President
Dr. Reddy's Research Foundation.